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Intracerebral Hemorrhage

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Keywords
Intracerebral hemorrhage · Epidemiology · Outcome · Pathophysiology · Risk factor · Treatment

Abstract
Background: Compared to ischemic stroke, intracerebral hemorrhage (ICH) has higher mortality and more severe disability. Asian such as Chinese and Japanese and Mexican Americans, Latin Americans, African Americans, Native Americans has higher incidences than do white Americans. So, ICH is an important cerebrovascular disease in Asia. ***Summary:*** ICH accounts for approximately 10–20% of all strokes. The incidence of ICH is higher in low- and middle-income than high-income countries and is estimated 8–15% in western countries like USA, UK, and Australia, and 18–24% in Japan, Taiwan, and Korea. The ICH incidence increases exponentially with age, and old age especially over 80 years is a major predictor of mortality independent of ICH severity. Females are older at the onset of ICH and have higher clinical severity than males. Modifiable risk factors include blood pressure, smoking, alcohol consumption, lipid profiles, use of anticoagulants, antiplatelet agents, and sympathomimetic drugs. Non-modifiable risk factors constitute old age, male gender, Asian ethnicity, cerebral amyloid angiopathy, cerebral microbleed, and chronic kidney disease. Blood pressure is the most important risk factor of ICH. Imaging markers may help predict ICH outcome, which include black hole sign, blend sign, iodine sign, island sign, leakage sign, satellite sign, spot sign, spot-tail sign, swirl sign, and hypodensities. ICH prognostic scoring system such as ICH scoring system and ICH grading scale scoring system in Chinese and Osaka prognostic score and Naples prognostic score has been used to predict ICH outcome. Early minimally invasive removal of ICH can be recommended for lobar ICH of 30–80 mL within 24 h after onset. Decompressive craniectomy without clot evacuation might benefit ICH patients aged 18–75 years with 30–100 mL at basal ganglia or thalamus. However, clinical studies are needed to investigate the effect of surgery on patients with smaller or larger ICH, ICH in non-lobar locations, and for older patients or patients with preexisting disability. Surgical treatment is usually associated with neurological sequels if survived. For medical treatment, blood pressure lowering should be careful titrated to secure continuous smooth and sustained control and avoid peaks and large variability in systolic blood pressure. Stroke and cancer are the most common causes of death in Asian ICH patients, compared to stroke and cardiac disease in non-Asian patients. ***Key Messages:*** The incidence and outcome are different between Asian and non-Asian patients, and more clinical studies are needed to investigate the best management for Asian ICH patients.

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Introduction

Globally, stroke was the second-leading cause of death and the third-leading cause of combined death and disability in 2019 [1]. It is estimated that ischemic stroke is the most common stroke subtype and occupied 62.4%

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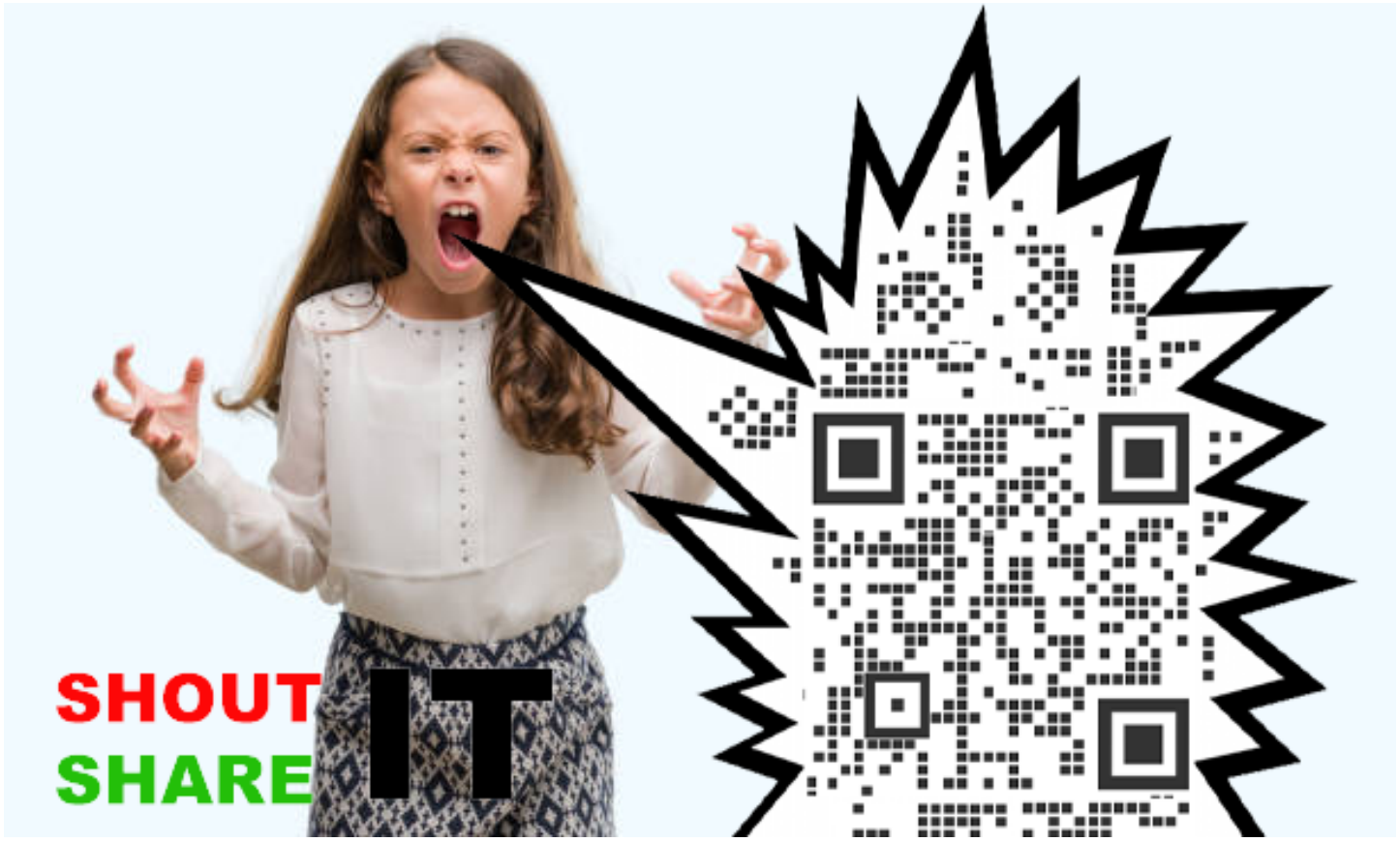
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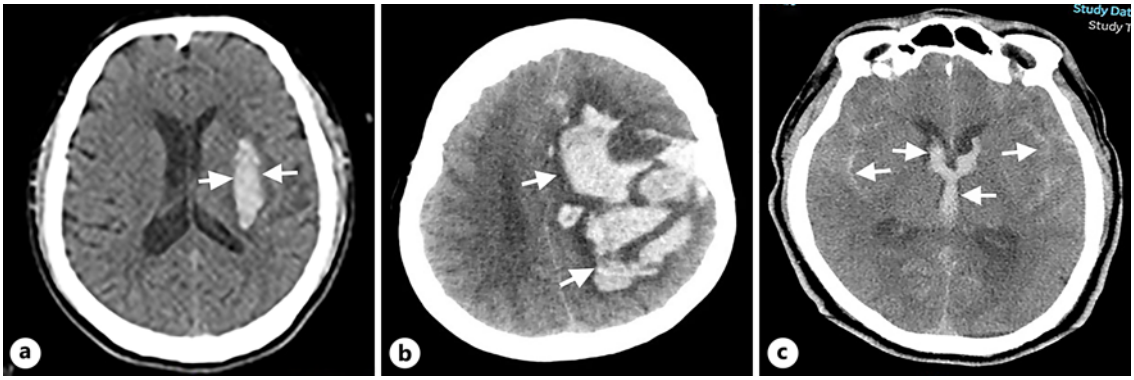

Fig. 1. Brain computed tomographic findings of the locations in different subtypes of intracranial hemorrhage. **a** Indicates hypertensive ICH at left putaminal area. **b** Indicates lobar hemorrhage at left frontal lobe. **c** Indicates subarachnoid hemorrhage with blood at subarachnoid space and intraventricular areas.

of all incident strokes, while intracerebral hemorrhage (ICH) constitutes 27.9% and subarachnoid hemorrhage constitutes 9.7% [1]. Ischemic lesions of small-vessel pathogenesis are frequently found in acute ICH, and primary ICH is known to share common risk factors and similar vascular pathology to mall vessel occlusion [2]. The occurrence of ICH is related to poor control of blood pressure (BP) and vascular anomaly that result in rupture of small penetrating arteries [3]. Compared to ischemic stroke, ICH has higher mortality and more severe disability [4]. With the improvement of BP control, the frequency of ICH has been reduced, but ICH is still an critical burden in developing countries [3].

Epidemiology

Low- and middle-income countries are known to have higher incidence of ICH than high-income countries, not only in the proportion of all strokes but also in absolute incidence rates [5]. The incidence rate of ICH in USA, UK, and Australia is estimated 8–15%, while 18–24% in Japan, Taiwan and Korea [3]. In USA, the incidence of ICH among Black is reported to be ≈1.6-fold greater than White people and 1.6-fold greater among Mexican American than non-Hispanic White people [6]. In China, the incidence and prevalence of strokes were 69.6% and 77.8% in ischemic stroke, 23.8% and 15.8% in ICH, 4.4% and 4.4% in subarachnoid hemorrhage, and 2.1% and 2.0% in undetermined type, respectively [7]. Mexican Americans, Latin Americans, African Americans, Native Americans, Japanese people, and Chinese people have higher incidences of ICH compared to white Americans [8].

Pathophysiology

In the initial injury stage, blood vessel rupture may result in hematoma formation which causes mechanical injury with compression of brain parenchyma by mass effect, resulting in physical disruption of parenchymal architecture. Secondary injury results in activation of microglia which releases detrimental substances causing blood-brain barrier dysfunction, vasogenic edema, and apoptosis in neurons and glia [9]. Intracranial pressure will be increased due to expansion of hematoma that can affect blood flow and cause mechanical deformation [3]. There are oligemia, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization [6].

Primary ICH may be due to high BP (hypertension) (Fig. 1a), cerebral amyloid angiopathy (CAA) (Fig. 1b), and subarachnoid hemorrhage (Fig. 1c). Hypertension is the main attributable risk factor for approximately 65% of ICHs. Secondary ICH is caused by brain tumors, aneurysms, arteriovenous malformations, cerebral cavernous malformations, and coagulopathy [10]. Most bleeding in hypertension-related ICH is at or near the bifurcation of small penetrating arteries that originate from basilar arteries or the anterior, middle, or posterior cerebral arteries [8]. The ruptured lesions are characterized by breakage of elastic lamina, atrophy and fragmentation of smooth muscle, dissections, and granular or vesicular cellular degeneration [11].

CAA is a common cause of symptomatic ICH and involves β-amyloid peptide deposition in the media of small- and medium-sized leptomeningeal and cortical vessels surrounding the vascular smooth muscle cells [12]. These weakened arteries may rupture and result in

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cerebral microbleeds or lobar ICH [13]. ICH in younger patients is more likely associated with vascular malformations, but in elderly patients more likely resulted from amyloid angiopathy. Deep-position ICH in the thalamus or basal ganglia is more likely due to hypertensive bleeds, irrespective of age [14].

Regarding anticoagulant-associated ICH, a meta-analysis of phase 3, randomized trials included data of all four new oral anticoagulants in patients with atrial fibrillation [15]. This meta-analysis demonstrated a favorable risk-benefit profile and revealed that new oral anticoagulants could reduce the events of stroke or systemic embolic by 19% compared to warfarin with a reduction mainly in hemorrhagic stroke. Also, new oral anticoagulants could significantly reduce all-cause mortality and intracranial hemorrhage but increase the frequency of gastrointestinal bleeding.

Risk Factors

Sex Difference

A literature review [16] found the epidemiology, risk factors, and management of spontaneous ICH could be different by sex. Males may experience spontaneous ICH more frequently than females at younger ages. The risk factors such as cocaine use, heavy alcohol use, and tobacco use are more common in males. Females experience more frequently lobar ICH, while both sexes have even distribution of deep ICH. Females receive less aggressive management than males, likely impacting survival.

A population-based registry of ICH [17] showed females were older at the onset of ICH and were found to have higher clinical severity with higher National Institutes of Health Stroke Scale (NIHSS) score at presentation than males. Also, the crude annual incidence rate of ICH showed it was 20.2 per 100,000 person-years in females but 30.2 per 100,000 person-years in males. Regarding 1-year case fatality rate, females had higher rate than males (48.5% vs. 40.1%), which was likely related to older age at ICH onset and higher NIHSS score in females [17].

Age

The incidence of spontaneous ICH increases exponentially with age [18]. In individuals aged >80 y/o, they represent a growing proportion of all people admitted to stroke units due to ICH. The incidence of ICH according to age showed the older the age, the higher the incidence.

Among young and middle-aged patients, females are related to a lower in-hospital mortality rate from ICH than males, and older male patients are at an increased risk of ICH complications which may contribute to higher in-hospital mortality [19]. Older ICH patients may have increased proportion of amyloid angiopathy and increased use of antithrombotic drug that result in lobar hemorrhage and cause a higher risk of hematoma enlargement [18]. Old age especially over 80 y/o is a major predictor of ICH mortality independent of characteristics related to ICH severity. As age increased, the length of hospital stay, financial burden, and mortality due to ICH increased. Older ICH patients have higher in-hospital mortality rate which could be related to pathogenesis, hematoma volume, antithrombotic use, and neuroinflammation [19].

The risk factors of ICH can be divided into modifiable risk factors, non-modifiable risk factors and other related factors [3]. Modifiable risk factors contain high BP, current smoking, severe alcohol consumption, low low-density lipoprotein cholesterol, low triglycerides, use of anticoagulants and antiplatelet agents and sympathomimetic drugs such as cocaine, heroin, amphetamine, phenylpropanolamine, and ephedrine. Sympathomimetic drugs are used more common in young patients. Phenylpropaolamine is suggested to be an independent risk factor for ICH, especially in females with either low or high dose [3]. Non-modifiable risk factors constitute old age, male gender, Asian ethnicity, CAA, cerebral microbleed, and poor renal function [3]. Other conditions that could be related to the risk of ICH may include multiparity, poor working conditions such as blue-collar occupation and long working time, and prolonged sleep duration [3].

APOE ε2 or ε4 genotype has strong association with lobar ICH. High BP is the most important risk factor for spontaneous ICH and is most related to deep-position ICH than lobar ICH [20]. High BP in deep-position ICH is twice as common as that in lobar ICH. High cholesterol level or moderate alcohol consumption (<=2 drinks per day) are less frequent in deep-position ICH [20]. There could be a protective association seen between high cholesterol level and deep-position ICH but no such association can be seen in lobar ICH [20]. An Australian case-control study showed high cholesterol levels may be associated with a reduced risk of ICH. Another study found that low total cholesterol and low-density lipoprotein cholesterol levels are associated with more severe ICH [21].

Warfarin may increase ICH risk by 2–5 folds if INR values >3.0 and is likely contributing to excess mortality

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[22]. In general population, aspirin was found not associated with ICH risk when compared to no aspirin, and chronic use of low-dose aspirin may be associated with a protective effect on SAH. However, a meta-analysis indicated that aspirin therapy could increase the risk of hemorrhagic stroke, but the overall benefit of aspirin on ischemic stroke may outweigh its adverse effects on the risk of hemorrhagic stroke [23].

Diabetes Mellitus

A review article found that there may be modest associations between diabetes and ICH occurrence and outcome, and a cohort study revealed ICH in diabetic patients usually presents different clinical features compared to ICH in nondiabetic patients, and diabetes could be an independent determinant of death after ICH [24].

Chronic Kidney Disease

Decreased glomerular filtration rate is a strong risk factor for hemorrhagic stroke, but not ischemic stroke in Rotterdam Study [25]. Chronic kidney disease is associated with a greater presence and number of cerebral microbleed in ICH patients, particularly in patients of black race [26]. Platelet dysfunction in patients with chronic kidney disease might also account for the increased risk of ICH [26].

Cerebral Microbleeds

Cerebral microbleeds may increase the risk of spontaneous ICH which is greater than the risk for recurrent ischemic stroke. Cerebral microbleeds may also increase the risk of warfarin or antiplatelet-associated ICH. Although European hospital cohort study of ischemic stroke patients showed cerebral microbleeds had a higher risk of future ischemic stroke, but not ICH, a large-scale prospective study in Japan found that cerebral microbleeds were more strongly associated with ICH than ischemic stroke [27].

Treatment of ICH

Surgical Treatment of ICH

The Early Minimally Invasive Removal of Intracerebral Hemorrhage (ENRICH) trial [28] suggests the minimally invasive trans-sulcal parafascicular surgery can be recommended for lobar ICH of 30–80 mL within 24 h after onset to reduce hematoma volume to <15 mL in patients aged 18–80 years without significant premorbid disability. The SWITCH study [29] is a randomized controlled trial of decompressive craniectomy comparing with medical treatment in patients with severe deep ICH within 72 h from stroke onset. SWITCH study suggested that decompressive craniectomy without clot evacuation might benefit ICH patients aged 18–75 years with 30–100 mL at basal ganglia or thalamus. However, it is still undetermined regarding the effect of minimally invasive surgery for patients with smaller or larger hematoma, for hematoma in non-lobar locations, and for older patients or patients with preexisting disability.

The guidelines of American Stroke Association [30] suggests ICH patients with hydrocephalus contributing to increased intracranial pressure, if there is a decreased level of consciousness, ventricular drainage should be performed to reduce mortality. In ICH patients with a reduced level of consciousness, intracranial pressure monitoring and treatment might be considered to reduce mortality and improve outcomes.

Medical Treatment of ICH

BP lowering in acute stage of ICH is beneficial to improve functional outcomes. BP should be careful titrated to secure continuous smooth and sustained control and avoid peaks and large variability in systolic BP [30]. BP lowering in acute ICH should be initiated as early as possible within 2 h of ICH onset, and BP target should be reached within 1 h to reduce the risk of hematoma expansion and improve functional outcome. In patients with mild to moderate severity of acute ICH, if systolic BP is 150–220 mm Hg, the target of BP should be lowered to below 140 mm Hg and maintained at 130–150 mm Hg to improve functional outcomes. Recent report suggests acute reduction to a target systolic BP of 110–139 mm Hg in acute ICH can be better in improving functional outcome than a reduction to a target systolic BP of 140–179 mm Hg. In patients with moderate to severe ICH, the target of acute BP lowering is not well established. However, intensive systolic BP lowering can reduce the frequency of hematoma expansion but does not reduce the rate of death or disability [30].

The mean absolute change of systolic BP is associated with hematoma growth, and a sustained BP control with a reduction in systolic BP variability is important to increase the beneficial effect of intensive antihypertensive treatment. To sustain BP control to minimize systolic BP variability, antihypertensive drugs which have rapid onset, short duration of action and easy titration are most suggested [30]. The ultra-acute use of venous vasodilators especially within 2 h may be harmful in acute ICH patients. The timing to initiate BP therapy and the optimal class of antihypertensive medication to achieve good BP control are still uncertain [30]. Bolus hyperosmolar therapy but not corticosteroids may be considered to reduce ICP transiently, and the efficacy of early prophylactic hyperosmolar therapy for improving outcomes is not well established [30].

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Neuroprotection

Statins are suggested to support the potential neuroprotection and enhance recovery in acute ICH [31]. The proposed mechanisms include promotion of angiogenesis, increased neurogenesis, inhibition of neuronal apoptosis, acceleration of hematoma resolution, decreased inflammation in the ICH boundary zone, and decreased perihematomal edema [31]. However, the studies of the relationship of statins to post-ICH outcomes are limited which precludes an objective assessment of the potential therapeutic benefits of statins in ICH patients.

Human serum albumin treatment is reported to provide neuroprotection and enhance recovery by improving short- and long-term neurologic function, maintaining blood-brain barrier integrity and reducing neuronal oxidative stress and apoptosis [32]. Admission low albuminemia is suggested to be a prognostic factor for poor outcomes in ICH patients [32]. However, the clinical trial was terminated due to low enrollment and its potential adverse effects.

Therapeutic hypothermia is suggested to reduce cell death mechanisms initiated by ICH. However, the current data for therapeutic hypothermia in ICH remains questionable despite the highly promising indications in animal studies [33]. Definitive randomized controlled studies are still required to answer this therapeutic question.

Outcome

ICH is a stroke subtype that is associated with high mortality and often have major neurological impairments if survived. Until now, there has been no successful Phase III clinical trial shown to improve the outcome of ICH [4]. Although ICH constitutes a relatively small percentage of the overall prevalence of stroke (approximately 10–15%), the associated morbidity and mortality are disproportionately high [34]. In-hospital mortality rates range from 27.1 to 37.5%, with 2-year mortality being as high as 49.5%. Only 14.5% of patients presenting with symptomatic ICH can be discharged home independently, but over 34% of symptomatic ICH patients were discharged to a long-term nursing care facility. In ICH, hematoma expansion and complications are the leading causes of death in early stage [34]. Poor prognostic factors of ICH may include low Glasgow coma scale score at presentation, ICH volume ≥30 cm^3, intraventricular hemorrhage, infra-tentorial localization of ICH, ≥80 y/o, advanced white matter lesions on brain image, low body weight and hyperglycemia at admission, and poor renal function with estimated glomerular filtration rate <60 mL/min/m^2 [3].

Radiology Findings

Hematoma expansion is a serious indicator to predict poor outcome and occurs in up to one-third of ICH patients [35]. Studies suggest hematoma expansion can be preventable using imaging markers. There are some specific markers on computed tomography (CT) and CT angiography (CTA) in the acute phase of ICH which is suggested to identify hematoma expansion early. These imaging markers include black hole sign, blend sign, iodine sign, island sign, leakage sign, satellite sign, spot sign, spot-tail sign, swirl sign, and hypodensities [35].

ICH Prognostic Scoring System

In Chinese population, the use of ICH scoring system and ICH grading scale scoring system has been found to accurately predict the short-term and long-term favorable functional outcome in ICH patients [36]. The ICH scoring system can also have a good predictive value in the prognostic evaluation of 30-day mortality for ICH patients taking oral anticoagulants, especially the use of non-vitamin K oral anticoagulants [36].

Osaka prognostic score (OPS) and Naples prognostic score (NPS) are established based on inflammatory and nutritional status. A cohort study showed if there were higher levels of OPS and NPS at admission, there was worse outcome at 6 months following ICH, suggesting the potential role of these scoring system to act as prognostic markers to predict ICH outcome [37].

Cause of Death

Using the combined data of stroke registry databank and Taiwan national death registry, our previous report demonstrated stroke is the leading cause of death not only in cerebral ischemia but also in cerebral hemorrhage (Table 1) [38]. Although cancer is the first leading cause of death in Taiwan, cancer is found to be the second or third-leading cause of death at 6 months after stroke onset in ischemic and hemorrhagic strokes even after excluding patients with cancer history [38]. Deaths within the first week are mostly due to the direct consequence of hemorrhagic injury, whereas deaths in the following weeks are mostly related to medical complications [39]. The comparison of cause of death in ICH among different countries showed in Asian, stroke and cancer are the most common causes of death, while in non-Asian [38], stroke and cardiac disease are the most common causes of death (Table 2).

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Table 1. Cause of death by hemorrhagic stroke subtypes (total = 2,742)

	Primary ICH n = 1,360 (49.6)		Secondary ICH n = 1,382 (50.4)		p value
Time	disease	n (%)	disease	n (%)	
Overall mortality		414 (30.4)		463 (33.5)	0.094
	Stroke	240 (58.0)	Stroke	304 (65.7)	
	Cancer	26 (6.3)	Diabetes	26 (5.6)	
30-day mortality		216 (15.9)		314 (22.7)	<0.001
	Stroke	179 (82.9)	Stroke	258 (82.2)	
	Diabetes	8 (3.7)	DAAC[1]	10 (3.2)	
1-year mortality		98 (7.2)		91 (6.6)	0.571
	Stroke	32 (32.7)	Stroke	34 (37.4)	
	Cancer	9 (9.2)	Cancer	10 (11.0)	
After 1-year mortality		100 (7.4)		58 (4.2)	<0.001
	Stroke	29 (29.0)	Stroke	12 (20.7)	
	Cancer	12 (12.0)	Diabetes	10 (17.2)	

Mortality rates were calculated from life table analysis. The table is adopted with the courtesy of professor Liu et al. [38]. ICH, intracerebral hemorrhage. p values using the χ^2 test. [1]Indicates diseases of arteries, arterioles, and capillaries (DAAC).

Table 2. Cause of death in patients with ICH among different countries

Data source	Region	Study period	N	Stroke			FU, years	Mortality, %	Cause of death in overall mortality			
				YS	FES	subtype			first	%	second	%
Hemorrhagic stroke												
Asian												
Liu et al.	Taiwan	2009–2011	877	–	+	Overall	5	32	Stroke	62	Cancer	6
Non-Asian												
Rutten-Jacobs et al.	Netherland	1980–2010	91	+	+	Overall	11.1	31.9	Cardiac	33	Stroke	22
Hansen et al.	Sweden	1996	323	–	–	Overall	13	82	Stroke	36	Cardiac	19
Fogelholm et al.	Finland	1985–1991	411	–	+	Overall	16	NA	Stroke	34	Cardiac	24
Combined ischemic and hemorrhagic strokes												
Asian												
Liu et al.	China	2002	752	–	+	Overall	1	13.6	Stroke	52	Cardiac	17
						LAA	1	15.8	Stroke	58	NA	NA
						SVO	1	7.3	Cardiac	33	NA	NA
						CE	1	11.9	Cardiac	32	NA	NA
						ICH	1	23.2	Stroke	NA	NA	NA
Sun et al.	Singapore	2000–2004	12,559	–	–		5	40.7	Stroke	35	Pneumonia	18
Non-Asian												
Hankey et al.	Australia	1989–1990	492	–	–		5	60.1	Cardiac	41	Stroke	15

The table is adopted with the courtesy of professor Liu et al. [38]. FU, follow-up period; Mortality, all-cause mortality; YS, young stroke; FES, first-ever stroke; SVO, small-vessel occlusion; LAA, large-artery atherosclerosis; CE, cardio-embolism; ICH, intracerebral hemorrhage; NA, not available.

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Risk of Recurrence

The risk of recurrent ICH ranges 1.2–3% per year across all ICH patients, and the first year after the incident ICH has the highest recurrent rate [30]. In patients with a primary ICH, the rate of recurrence, vascular death, or vascular events is estimated 2.1%–5.9% annually. In ICH patients aged ≥65 years, there is doubled the risk of recurrence, vascular event, or death. Asian and Black ICH patients have a higher risk of recurrent event than white patients, and patients with private insurance have reduced risk compared to those with Medicare [40]. In ICH patients, less than half of patients can survive 1 year and less than a third survive 5 years. After ICH, the risk of either recurrent ICH or recurrent ischemic stroke appears similar [30].

Secondary Prevention

It is advisable to incorporate the following risk factors to prevent ICH recurrence: (a) lobar location of the initial ICH; (b) older age; (c) presence, number, and lobar location of microbleeds on MRI; (d) presence of disseminated cortical superficial siderosis on MRI; (e) poorly controlled hypertension; (f) Asian or Black race; and (g) presence of apolipoprotein E ε2 or ε4 alleles [30].

Conclusion

The incidence, risk factors, and cause of death in ICH patients are different among ethnicities and genders. Medical treatment needs intensive control of BP, and minimally invasive surgery can be considered for lobar ICH within 24 h after onset. ICH carries high mortality, and there are major neurological impairments if survived. ICH is a critical disease, and more studies are needed to improve patient outcomes.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

T.-H.L. contributed to the manuscript draft, the conception and design of the work, manuscript revision and supervision for critically important intellectual content.

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